VETERANS HEALTH ADMINISTRATION
OFFICE OF PATIENT CARE SERVICES
TECHNOLOGY ASSESSMENT PROGRAM

BRIEF OVERVIEW:

SYSTEMATIC REVIEWS
FOR LOCALIZED PROSTATE CANCER

Prepared by
Karen Flynn, DDS, MS

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TECHNOLOGY ASSESSMENT PROGRAM

An Effective Resource for Evidence-based Managers

VA's Technology Assessment Program (TAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in VA. TAP responds to the information needs of senior VA policy makers by carrying out systematic reviews of the medical literature on health care technologies to determine "what works" in health care. "Technologies" may be devices, drugs, procedures, and organizational and supportive systems used in health care. TAP reports can be used to support better resource management.

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All TAP products are reviewed internally by TAP's physician advisor and, where appropriate, key experts in VA. Additional comments and information on this report can be sent to:

VA Technology Assessment Program • Office of Patient Care Services
Boston VA Healthcare System (11T) • 150 S. Huntington Ave. • Room JP9-321
Boston, MA 02130 • Tel. (857) 364-4469 • Fax (857) 364-6587 • VATAP@va.gov

A SUMMARY FOR HTA REPORTS
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VATAP is a member of the International Network of Agencies for Health Technology Assessment (INAHTA) [www.inahta.org]. INAHTA developed this checklist© as a quality assurance guide to foster consistency and transparency in the health technology assessment (HTA) process. VATAP has added this checklist to its reports produced since 2002.

This summary form is intended as an aid for those who want to record the extent to which a HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

Brief Overview:
Systematic Reviews for Localized Prostate Cancer
September 2009

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?	√		
4. Statement on whether report externally reviewed?	√		
5. Short summary in non-technical language?			√
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of the assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?			√
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

CONTRIBUTORS TO THIS REVIEW

Notes:

- **TAP projects draw on expertise within VHA nationally.**
- **All TAP products acknowledge multiple contributors.**
- **No contributors report conflicts of interest.**

TAP staff person/position	Role	Responsibilities
Karen Flynn Program Manager Boston	Primary author	Conception and conduct of review: • Communication with client; • Interim information; • Analytic framework; • Draft review; • Final review.
Elizabeth Adams Health System Specialist Boston	Consultation throughout project	Internal content and format of draft and final report.
Elaine Alligood Information Specialist Boston	Literature database searches	Database searches: • Design strategy; • Choose/manage databases; • Strategy text and references for report; • TAP library/archive of information resources.
Bernard Spence Administrative Officer Boston	Administrative support	• Budget/resources; • "Intelligent lay reader" review; • Project tracking.
Rebecca Morton Library Technician Boston	Article retrieval	Information retrieval: • Full text from print journals and electronic resources; • Manage reference lists.
Valerie Lawrence Physician Advisor San Antonio	Content and methods review	Final review: • Internal consistency; • Clarity; • Clinical context; • Methods.
Andrea Gwosdow, Ph.D. **Cherie Dewar** Gwosdow Associates Boston	Freelance medical writers	Final review: • Clarity; • Copyediting.

ABBREVIATIONS IN THIS REVIEW

3D-CRT, three-dimensional conformal radiation therapy
ABS, American Brachytherapy Society
ADT, androgen deprivation treatment
AHRQ, Agency for Healthcare Research and Quality
AHT, adjuvant hormonal therapy
ANN, artificial neural network
AR, adjuvant radiotherapy
AUA, American Urological Association
AUASI, American Urological Association Symptom Index
AUC, area under the curve
bNED, biochemical no evidence of disease
bPF(S), biochemical progression free (survival)
BT, brachytherapy
CAG, cytosine, adenine, guanosine (nucleotides)
CAM, complementary/alternative medicine
CaP, prostate cancer
CAPRA, Cancer of the Prostate Risk Assessment (scale)
CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor (registry)
CCOHTA, Canadian Coordinating Office for Health Technology Assessment
CI, 95% confidence interval
CNS, central nervous system
CPG, clinical practice guideline
CSS, cause-specific survival
CT, computed tomography
DES, diethylstilbesterol
DFS, disease-free survival
DOR, diagnostic odds ratio
DRE, digital rectal exam
DVH, dose volume histogram
EAU, European Association of Urology
EB, evidence-based
EBRT, external beam radiation therapy
ECOG, Eastern Cooperative Oncology Group
ED, erectile dysfunction
EORTC, European Organization for Research and Treatment of Cancer
EPE, extra-prostatic extension (pathology)
ER/D, emergency room/department
ERSPC, European randomized study of screening for prostate cancer
FFF, freedom from failure
FU, follow-up
GI, gastro-intestinal
GS, Gleason score
GU, genitourinary
Gy, gray (radiation unit)
HDRBT, high dose rate brachytherapy
HIFU, high intensity focused ultrasound
HR, hazard ratios
HRQoL, health-related quality of life
HT, hormone therapy
HTA, Health Technology Assessment (UK)
IBD, inflammatory bowel disease
ICER, Institute for Clinical and Economic Review
IMRT, intensity-modulated radiation therapy
INAHTA, International Network of Agencies for Health Technology Assessment
IPCA, insignificant prostate cancer
IPSS, International prostate symptom score
IQWiG, Institut für Qualität und Wirtshaftlichkeit im Gesundehheitswesen (Germany)
ITT, intention to treat
LOS, length of stay
LRP, laparoscopic radical prostatectomy
M0, M category of prostate cancer (The cancer has not spread beyond the regional lymph nodes.)
MRI, magnetic resonance imaging
MRS, magnetic resonance spectroscopy
N0, N category of prostate cancer (The cancer has not spread to any lymph nodes.)
NAAD, neoadjuvant androgen deprivation
NG, nomogram

NHS, National Health System (UK)
NHT, neoadjuvant hormonal therapy
NICE, National Institute for Clinical Excellence (UK)
NIH, National Institutes of Health (US)
NPV, negative predictive value
NS, not (statistically) significant
NSRP, nerve sparing radical prostatectomy
OPCS, Office of Patient Care Services
PB, prostate brachytherapy
PBT, proton beam therapy
PCPT, prostate cancer prevention trial
PCSI, prostate cancer symptom index
PDE(5), phospho-diesterase (5)
PFMT, pelvic floor muscle training
PIVOT, Prostate cancer Intervention Versus Observation Trial
PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PPV, positive predictive value
PSA, prostate specific antigen
PSAV, prostate specific antigen velocity
QALY, quality-adjusted life year
QoL, quality of life
RALP, robot-assisted laparoscopic radical prostatectomy
RCT, randomized controlled trial
ROC, receiver operating characteristic
RP, radical prostatectomy
RR, relative risk
RRP, retropubic radical prostatectomy
RT, radiation therapy
RTOG, Radiation Therapy Oncology Group
SBU, Swedish Council on Technology Assessment in Health Care
SD, sexual dysfunction or standard deviation, depending on context
Se, sensitivity
SEER, Surveillance, Epidemiology and End Results
SF-36, Short form health survey-36 item
SIGN, Scottish Intercollegiate Guidelines Network
SINTEF, Norwegian Center for Health Technology Assessment
SMD, standardized mean difference
Sp, specificity
SPCG-4, Scandinavian Prostate Cancer Study Group Number 4
SWOG, Southwest Oncology Group
TAAG, Technology Assessment Advisory Group (VHA OPCS)
TNM, tumor-node-metastases
TRUS, trans-rectal ultrasound
TURP, trans-urethral resection of prostate
UCLA, University of California at Los Angeles
UI, urinary incontinence
UK, United Kingdom
UROG, Uro-oncology Research Group
US(A), United States (of America)
USPSTF, United States Preventive Services Task Force
VA, Veterans Administration
VACURG, Veterans Administration Cooperative Urological Research Group
VATAP, VA Technology Assessment Program
WMD, weighted mean difference
WW, watchful waiting

BRIEF OVERVIEW:
Systematic Reviews for Localized Prostate Cancer

BACKGROUND

VHA's TAAG asked the VATAP for a review of the literature as support for use of brachytherapy for men with localized prostate cancer. Brachytherapy (BT) is one of several treatment options for localized prostate cancer.

The following quotations from the recent literature indicate the complex overlapping of several issues in the context of localized prostate cancer management, none of which can be addressed effectively in isolation from the others:

> *"Prostate cancer is the most common noncutaneous malignancy and the second leading cause of death in men. Ninety percent of men with prostate cancer are over aged 60 years, diagnosed with the prostate specific antigen (PSA) blood test and have disease believed to be localized to the prostate gland (clinically localized). Common treatments for clinically localized prostate cancer include watchful waiting and surgery to remove the prostate gland (radical prostatectomy), external beam radiation therapy and interstitial radiation therapy (brachytherapy). Little is known about the relative effectiveness and harms of treatments due to the paucity of randomized controlled trials. The VA/NCI/AHRQ Cooperative Studies Program Study #307: Prostate Cancer Intervention Versus Observation Trial (PIVOT), initiated in 1994, is a multicenter randomized controlled trial comparing radical prostatectomy to watchful waiting in men with clinically localized prostate cancer."* (Wilt, 2009).
>
> *"Prostate cancer is a clinically heterogeneous disease. A substantial proportion of prostate cancer cases detected with current screening methods will never cause symptoms during the patients' lifetime. Modeling studies based on U.S. incidence data suggest over-diagnosis rates ranging from 29% to 44% of all prostate cancer cases detected by PSA screening. Because patients with "pseudo-disease" receive no benefit from, and may be harmed by, prostate cancer screening and treatment, prostate cancer detection in this population constitutes an important burden…*(The USPSTF statement in *2002)…found insufficient evidence that screening for prostate cancer improved health outcomes, including mortality…It also found little evidence on the harms of the screening process or the natural history of prostate cancer cases detected with screening."* (USPSTF, 2008).
>
> *"…because of the difficulties in identifying this group of patients* (men with indolent cancers who are unlikely to experience symptoms) *the majority do receive radical local treatment, which can result in erectile dysfunction and urinary leakage. The problem for clinicians is deciding which men have fast-growing cancers that need essential treatment and which men have slow-growing cancers that will never trouble them. Prognostic markers may help to avoid unnecessary treatment and identify patients with poor outcomes who would be candidates for trials of adjuvant treatment."* (Sutcliffe, 2009).
>
> *"Why is prostate cancer screening so difficult? Simply put, because it attempts to mitigate a disease of which we have a poor understanding by using a test not well suited to the job (a positive PSA result in the ranges used for screening has a likelihood ratio of 2). The stage migration seen in prostate cancer over the past 20 years is certainly remarkable. However, rates of over-diagnosis have been estimated at 20% to 50% for a disease with a current annual incidence >186,000 in the USA alone. Side effects of*

> *treatment can be considerable and may include lasting effects on urinary, bowel, sexual, and vitality functions. Unfortunately even patients with clear evidence of indolent disease, who are candidates for surveillance, suffer from cancer diagnosis. Indeed, the most common reason patients stop surveillance and have active treatment is anxiety, not disease progression."* (Canfield, 2009).

Prostate cancer classification and risk assessment is essential context information here:

Table 1. Tumor-Node-Metastases (TNM) classification system for prostate cancer*

Note: Darker shading indicates tumor (T) categories; lighter stages are generally, although not invariably, considered to comprise "clinically localized".

Stage	Definition
T1: Clinically inapparent tumor, neither palpable nor visible	
T1a	Incidental finding in< 5% of tissue resected during TURP
T1b	Incidental finding in > 5% of tissue resected during TURP
T1c	Identified by needle biopsy initiated by elevated PSA
T2: Tumor confined within the prostate	
T2a	One lobe involved
T2b	Both lobes involved
T3: Tumor extends through capsule or present at resection margin (R1)	
T3a	Unilateral or bilateral extra-capsular extension
T3b	Seminal vesicles involved
T4: Fixed or invades adjacent structures	

***Adapted from Crook (2001) and Morgan (2008)

Gleason score (Table 2) is a system of grading prostate cancer based on its microscopic appearance. It indicates the sum of predominant histological pattern (graded 1 to 5) and the next most common pattern. Gleason scores range from 2 to 10, indicating how likely a tumor will spread. The higher the score is, the higher the likelihood of spread. Biopsy specimens (versus those from radical prostatectomy) provide insufficient tissue for complete Gleason scoring and cannot be scored lower than 6 (3 + 3).

Table 2. Risk stratification for localized prostate cancer*

Risk	PSA (ng/ml)	Gleason	TNM Stage
Low	<10	≤6	T1-T2a
Intermediate	10-20	7	T2b-T2c
High	>20	8-10	T3-T4

* Adapted from Graham (2009)

Analytical framework: Systematic reviews

> *"Healthcare providers, consumers, researchers, and policy makers are inundated with unmanageable amounts of information. We need systematic reviews to efficiently integrate valid information and provide a basis for rational decision making. Systematic reviews established where the effects of healthcare are consistent and research results can be applied across populations, settings, and differences in treatment (e.g., dose); and where effects may vary significantly…*
>
> *Wide recognition of the key role of reviews in synthesizing and disseminating the results of research has prompted people to consider the validity of reviews. In the 1970s and*

> *early 1980s, psychologists and social scientists drew attention to the systematic steps needed to minimize bias and random errors in reviews of research. It was not until the late 1980s that people drew attention to the poor scientific quality of healthcare review articles. However, recognition of the need for systematic reviews of healthcare has grown rapidly and continues to grow…"* (Mulrow, 1997).

Regarding treatments for localized prostate cancer, the universal localized disease perspective mandated an overview of available systematic reviews, guidelines based on such reviews, and economic evaluations using high quality primary studies or reviews as sources of effectiveness data. This document will refer collectively to these synthesis publication types as "reviews".

Systematic reviews qualify as reproducible science. Cook (1997) and Mulrow (1997) define systematic reviews: "*Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their "subjects". They synthesize the results of multiple primary investigations by using strategies that limit bias and random error…"*

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria, and thus do not qualify as reproducible unbiased science. Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;
- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to summarize study results) or qualitative; in either case, the inferences or conclusions of the review must follow logically and specifically from the evidence presented. The rigor of this approach is illustrated by the placement of systematic reviews in evidence grading schemes (Cook 1995; Guyatt 1995; Sullivan 2005), where they receive the highest level designation. Reviews produced by the Cochrane Collaboration (www.cochrane.org) set the standard for rigor of methods and validity of conclusions. Cochrane reviews are meta-analytic where primary studies permit.

A catalog of reviews provides an immediately accessible overview of the state of the research literature by highlighting those research questions for which a quantity and presumably quality sufficient to warrant review has been published. Such a catalog also synthesizes a larger body of literature than otherwise would be feasible for any single review, while defining gaps in the knowledge base for a research agenda. Reviewers may find insufficient quantity or quality of published research to definitively answer their questions, but rigorous methods make even apparently negative findings valuable to understanding the knowledge base.

Review production assumes a threshold level of available primary research tailored to the review question. Conversely, the lack of published high-quality reviews indicates a corresponding lack of published research on issues of interest to the TAAG.

METHODS

VATAP first identified available systematic reviews and technology assessments for localized prostate cancer. VATAP then updated searches conducted by review authors to confirm the

presence or absence of subsequently published eligible primary studies that would change review conclusions. Since multiple high quality reviews cover pre-2000 literature, VATAP focused on post-2000 literature.

Search strategy/selection criteria

In July 2009, VATAP repeatedly searched Medline, the Cochrane Library, and INAHTA databases using the terms "localized prostate cancer", or "brachytherapy" along with publication types (systematic review, meta-analysis, economic evaluation) to identify full-text reviews published in English from 2000 to 2009 that synthesized clinical research, and involved adult human patients. Searches for subsequently published review-eligible studies (eligibility criteria specific to each review as detailed in the Appendix) were conducted in August 2009 and all searches were finally updated on September 10, 2009.

VATAP excluded:

- Narrative reviews, opinion pieces, and other publications lacking primary clinical data;
- Reviews or primary studies focused on treatment of advanced disease;
- Articles already included in systematic reviews;
- Studies available only as abstracts;
- Studies comparing within-treatment-category technical variations;
- "Quasi-systematic" reviews, i.e., those indexed or titled as systematic but which, on close examination, do not meet criteria or are inadequately reported to judge.

RESULTS

Table 3 outlines the 19 available reviews (excluding duplicate publications), covering primary studies from publication years 1966 to 2007 (updated here to September, 2009), for management of localized prostate cancer and related issues.

Appendix Table 5 abstracts these reviews in detail, along with subsequently published review-eligible primary studies, none of which alter review conclusions.

Table 3. Systematic reviews for localized prostate cancer*

Note: Light shading indicates related or duplicate reviews: same review in different formats or publications; e.g.: multiple NICE documents provide sequentially dated evidence reviews, guidance/guidelines for NHS, and abstracts for professionals or patients; or print journal publication of AHRQ evidence review.

Citation	Publication years covered	Content
Treatment options including brachytherapy		
Wilt (AHRQ; 2008b)	-2007	Effectiveness and harms of treatments for clinically localized prostate cancer
Wilt (2008a)	-2007	Effectiveness and harms of treatments for clinically localized prostate cancer
Veldeman (2008)	-2007	IMRT for prostate and other cancers
Shelley (Cochrane; 2007)	-2006	Cryotherapy
IQWiG (2007)	-2006	Interstitial brachytherapy in localized prostate cancer: review in German with English summary
Alibhai (2004)	1966-2003	RCTs in localized prostate cancer
Graham (2009)	Summary of NICE (2008)	Diagnosis and treatment
NICE (2008)	1950-	Full guideline: diagnosis and treatment of prostate cancer
NICE (2006a; 2006b)	1966-2005	High dose rate brachytherapy + EBRT
NICE(2005b)		Low dose rate brachytherapy
NICE (2004; 2005a)	1966-February 2004	High-intensity focused ultrasound
Hummel (NHS; 2003)	1966-2002: 16 RCTs	Clinical and cost-effectiveness of new and emerging technologies
Norderhaug (2003)	1966-2000	Brachytherapy for prostate cancer
CCOHTA (2002); pre-assessment	-2002: 9 available assessments/ systematic reviews	Brachytherapy for localized prostate cancer
Crook (2001)	1988-99	Brachytherapy for localized prostate cancer
SBU (2000); alert	-2000: descriptive studies in Sweden	Brachytherapy for prostate cancer
Other relevant reviews		
Sutcliffe (2009)	March-April 2007	Biomarkers as prognostic risk factors
Vickers (2009)	-2007	Pre-treatment PSA dynamics as predictors for cancer
Wilt (2008c)	1980-2007	Hospital and surgeon volume-outcome association for radical prostatectomy
Hövels (2008)	1980-2004	Diagnostic accuracy of CT and MRI in staging pelvic lymph nodes
Schröder (2008)	-2007	Models for predicting risk of positive biopsy with PSA alone
Candy (2008)	Abstract of Miles (2007)	
MacDonald (2007)	1966-2006	Pelvic floor muscle training for urinary incontinence after RP
Miles (Cochrane; 2007)		Interventions for SD secondary to prostate cancer treatment
Ilic (2007)	Abstract of Ilic (2006); below	
Ilic (Cochrane; 2006)	-2005: 2 RCTs	Screening for prostate cancer
	Total	• **19 reviews for localized prostate cancer treatment; 4 related/duplicate publications**

***** Including reviews for other aspects of localized prostate cancer: screening; risk assessment.

SUMMARY/DISCUSSION

Reviews covering the available, overwhelmingly observational, evidence for localized prostate cancer generally concur that the management options appear to be fundamentally equivalent in terms of survival outcomes. Patients and their physicians thus choose among options based on adverse event profiles or biochemical outcomes, convenience, and other factors not exclusively related to survival. The current research evidence base is inadequate to definitively determine the best treatment option, among them brachytherapy, with the optimal balance of benefits and harms for well-defined groups of patients. Complete, isolated randomized controlled trials (RCTs) and others in progress, such as VHA's PIVOT, may reach a critical mass of rigorous studies to clarify some issues in the foreseeable future.

Two additional and related core questions remain: *Do the benefits of organized population or opportunistic PSA screening outweigh harms? Which screen-detected cancers are likely to pose significant problems for their owners?*

Large screening trials are within reach of final results, but interim analyses of endpoints other than primary mortality endpoints [Appendix; Table 5, entries following Ilic, (2006)] have not silenced controversy. VATAP notes inconsistencies in trial protocols along with results. Optimal screening protocols (e.g., PSA cut points, screening intervals, and contributions of DRE) remain to be fully defined.

Research into predictive models and biomarkers continues [Appendix entries following Vickers (2009) and Schröder (2008)], but those currently available are imperfect for definitive assignment of insignificant cancer status with watchful waiting rather than immediate active or invasive treatment. PSA kinetics may seem intuitively sensible but have produced mixed results in research use. The long list of predictive models, specificity to single treatments or derivation populations, and lack of external validation no doubt complicate clinical use.

Summaries of available evidence by Alibhai (2004) and Norderhaug (2003), both in the Appendix, remain essentially unchanged by subsequently published research:

> *"...Each active treatment option has associated short-term morbidity and long-term consequences such as incontinence and erectile dysfunction. For the majority of these options, there are no randomized trials demonstrating any advantage in clinically important endpoints such as disease-specific mortality. Conversely, existing evidence from case-series and cohort studies generally suggests similar biochemical control and overall survival, regardless of which treatment is selected…"* (Alibhai, 2004).

> *"Prostate cancer patients face the choice among three different treatment options* (RP, EBRT*,* and BT*) each with questionable documentation about clinical effectiveness. Knowing that the advice from the consulting physician is considered most important in the decision making process, the key question is what advice do physicians give. A survey comparing treatment recommendation by urologist and oncologists in the treatment of localized prostate cancer showed that most urologists recommended radical prostatectomy while oncologists recommended external beam radiation. Although there were few studies on patients' preferences, expectations for clinical effect and complications did influence the treatment decision. The availability of the actual treatment may also influence choices…for some patients, especially those living far from hospitals providing EBRT, the possibility of having a quick outpatient treatment may seem attractive…Radical prostatectomy is a rather extensive surgical intervention that requires hospitalization…"* (Norderhaug, 2003).

Finally, like VHA, the UK's NHS advocates patient-centered care for men with prostate cancer (NICE, 2008):

> *"Healthcare professionals should adequately inform men with prostate cancer and their partners or carers about the effects of prostate cancer and treatment options on their sexual function, physical appearance, continence and other aspects of masculinity. Healthcare professionals should support men and their partners or carers in making treatment decision, taking into account the effects on quality of life as well as survival.*
>
> *To help men decide whether to have a prostate biopsy, healthcare professionals should discuss with them their prostate specific antigen (PSA) level, digital rectal examination (DRE) findings (including an estimate of prostate size) and comorbidities, together with their risk factors (including increasing age and black or Caribbean ethnicity) and any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy.*
>
> *Men with low-risk localized prostate cancer who are considered suitable for radical treatment should first be offered active surveillance.*
>
> *Men undergoing radical external beam radiotherapy for localized prostate cancer should receive a maximum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.*
>
> *Healthcare professionals should ensure that men and their partners have early and ongoing access to specialist erectile dysfunction services.*
>
> *Healthcare professionals should ensure that men with troublesome urinary symptoms after treatment have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include coping strategies, along with pelvic floor muscle re-education, bladder retraining and pharmacotherapy.*
>
> *Healthcare professionals should refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter.*
>
> *Biochemical relapse (a rising PSA) alone should not necessarily prompt an immediate change in treatment.*
>
> *Hormonal therapy is not routinely recommended for men with prostate cancer who have biochemical relapse unless they have: symptomatic local disease progression, or any proven metastases, or a PSA doubling time < 3 months.*
>
> *When men with prostate cancer develop biochemical evidence of hormone-refractory disease, their treatment options should be discussed by the urological cancer multidisciplinary team (MDT), with a view to seeking an oncologist and/or specialist palliative care option, as appropriate.*
>
> *Healthcare professionals should ensure that palliative care is available when needed and not limited to the end of life. It should not be restricted to being associated with hospice care."*

Chen (2009b) and Cooperberg (2009) reiterate similar principles, confirming the current status of the literature:

> *"The Institute of Medicine and the National Cancer Institute have identified quality of life in cancer survivors and "patient-centered communication" as priority research areas. These issues intersect in the more than 180,000 men annually diagnosed in the United States with clinically localized prostate cancer, nearly all probable long-term survivors, who must choose among treatment options that may profoundly affect their quality of life*

(QOL). Although the three major treatment modalities, radical prostatectomy (RP), external-bean radiation therapy (EBRT) and brachytherapy (BT) have currently indistinguishable efficacy, more than a decade of increasingly sophisticated QOL research has established their distinctive effects on urinary, bowel, and sexual function…" (Chen, 2009b).

"Counseling men with a new diagnosis of prostate cancer entails many challenges including presentation of realistic likelihoods of disease progression and mortality. These likelihoods, together with patient comorbidity, life expectancy, and preferences for treatment, should help guide planning of a risk-adapted treatment strategy. Men with low-risk prostate cancer are now eligible for at least a trial period of active surveillance at a growing number of institutions. Men with low- to intermediate-risk disease are well managed by local monotherapy, while those with higher risk disease generally require aggressive multimodal treatment. Finally, men with high-risk tumors are treated systemically for presumptive metastatic disease and/or, ideally, should be offered clinical trial enrollment, given the high rates of recurrence and progression with extant standard therapies." (Cooperberg, 2009).

IN-PROGRESS RESEARCH

As noted below, only two studies indexed in the NIH database for ongoing trials can be expected to contribute further evidence to the core reviews above.

Table 4. In-progress studies

Retrieved from www.clinicaltrials.gov on August 26, 2009 using "localized prostate cancer".
Listed: in progress trials, recruiting or not; trials comparing major treatment options.
Not listed: completed or withdrawn; trials testing technical variations of interventions.

Name/Purpose	Sponsor/location	Design/outcomes	Estimated completion
PIVOT	DVA, AHRQ, NCI Multiple centers	RCT: mortality	2010
Active surveillance, radical prostatectomy, or radiation therapy in treating patients with localized prostate cancer	Oxford Radcliffe Hospital (UK)	RCT: survival, QoL, costs	2013

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APPENDIX

Table 5. Systematic reviews and technology assessments: clinically localized prostate cancer

Note--Review entries listed in Table 3 are bolded within shaded cells. Subsequently-published eligible studies not listed in Table 3 are not bolded and within clear cells.

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
Treatment options including brachytherapy		
Morgan (2008)	**What is the optimal approach to positive radical prostatectomy margins?** **Adjuvant radiotherapy or active surveillance:** • Multiple databases, 1980-2008; • English-language RCTs enrolling pT3 or R1 stage prostate cancer patients initially treated with any RP approach; • Quality assessment: randomization; blinding; descriptions of withdrawals; ITT analysis; • Meta-analysis with Cochrane software planned, where data available from ≥ 2 trials; • Outcomes: overall survival; disease-specific survival; bPF survival; locoregional recurrence free survival; time to initiate AHT; acute and late toxicity; QoL.	**3 RCTS (1743 patients):** • 2 trials reporting overall survival: NS difference with AR (HR, 0.91; CI, 0.67-1.22); • All trials reported bPF survival: AR significantly improved (HR, 0.47; CI, 0.40-0.56; p<0.00001); • One trial reported comparative graded toxicity: NS difference between arms in severe (≥ grade 3) GI or GU toxicity at 5 years. **Conclusions:** *"To date, adjuvant RT has not been shown to improve overall survival compared with active surveillance. Longer follow-up from completed RCTs is required to accurately assess this outcome. Adjuvant RT does, however, significantly improve bPFS and is not associated with excess severe late toxicity."*
NICE (2008)	**Clinical guideline** **Diagnosis and treatment of prostate cancer:** • Multiple databases. 1950 onward; guided by guideline questions and without language restrictions; • Included: "papers published or accepted for publication in peer-reviewed journals", restricted to systematic reviews, RCTs, or economic evaluations where possible; critical appraisal by SIGN checklist.	Guideline presents evidence in tabular and algorithm form: full guideline available at www.nice.org.uk. **Implementation recommendations** quoted in Summary section (page7) above; **Research recommendations:** • *"Further research is required into the identification of prognostic indicators in order to differentiate effectively between men who may die with prostate cancer and those who might die from prostate cancer.* • *The greatest uncertainties are around the identification of which cancers are of clinical significance and over the choice of radical treatment, and in which settings they are appropriate.* • *With the diagnosis of prostate cancer being made more frequently in asymptomatic men, it is of growing importance to know which of these men are likely to benefit from aggressive treatment.* • *Research is required into the clinical and cost effectiveness of treatments aimed at the elimination of disease in men with localized prostate cancer, with locally advanced disease and with locally recurrent disease. This research should include a rigorous examination of procedures such as brachytherapy (localized disease only), cryotherapy and high intensity focused ultrasound, as well as combinations of surgery and radiotherapy with hormonal therapy and chemotherapy. The endpoints should include survival, local recurrence, toxicity and quality of life.*

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
		A wide and growing range of radical therapies aimed at the eradication of disease are available. Although longer term follow-up data for some of these in the localized disease setting, there have been no randomized trials comparing these treatments and there is little evidence to support their use in locally advanced disease or localized recurrent disease."
Graham (2009)	*See NICE (2008), immediately above.*	
Veldeman (2008)	**What level of evidence supports the use of IMRT for various disease sites?** ***Head and neck; prostate; gynecologic; CNS; breast; GI:*** • *Medline and Embase to August 2007;* • *Clinical studies reporting: overall survival; disease-specific survival; QoL; treatment-induced toxicity or surrogate endpoints.*	**16 studies for prostate cancer:** Comparable case series (most with historical controls): heterogeneous regarding target volume definition; margin size; organs at risk, dose-volume constraints.; fractionation; and radiation techniques; **VATAP comments:** • Unfocussed research question, non-specific inclusion criteria, and lack of quality assessment make this review almost quasi-systematic but it does adequately represent the status of the literature as restricted to high-risk-of-bias case series with historical controls. • Authors' conclusions below should be viewed with caution. **Conclusions:** *"Consistency in the findings of comparative studies and predictions from planning studies (external validity) allow the conclusion to be made that IMRT, on its own or as a component of improved radiotherapy techniques, create a window for dose escalation with unchanged or lower gastrointestinal and genitourinary toxic effects and unchanged or better sexual function."*
Wilt (2008b) AHRQ	**Comparative effectiveness and harms of treatments for clinically localized prostate cancer:** • **Comparative short- and long-term benefits and harms;** • **How patient and tumor characteristics affect outcomes, overall and differentially.** • Multiple databases; -2007; • Included: studies enrolling men with stage T1 or T2 disease, randomly allocated to any treatment for prostate cancer (any language); stage T3 or T4 if outcomes reported separately for localized disease; • nonrandomized in English (published1991-2004); • Excluded: < 50 patients; did not report or stratify outcomes for localized disease; • Outcomes: all-cause and disease-specific mortality; biochemical and clinical progression; averse events; patient satisfaction; **Evidence evaluation:** • Quality assessment for RCTs: allocation concealment; length of FU; drop out rate; loss to FU; • Strength of evidence: consistent results from ≥2 high	**Description of included studies (18 RCTs and 473 observational):** • No treatment option had consistent results from at least 2 high quality RCTs with adequate FU and statistical power; • 3 RCTs compared major treatment categories (RP Vs RT or WW) and no trials enrolled men with primarily PSA-detected disease; • Many RCTs were inadequately powered to provide long-term survival outcomes; most reported biochemical progression or recurrence as main outcomes; • No RCT evaluated cryotherapy, laparoscopic, or robotic-assisted RP, primary androgen deprivation, high intensity focused ultrasound, proton beam, or intensity modulated radiation; • Non-randomized studies varied widely in treatment effectiveness and harms, definitions and reporting of outcomes; • Many studies included patients with locally advanced disease but did not analyze separately by stage. **Results from 18 RCTs and 1 pooled analysis of 3 trials:** • 14,595 patients total; • 15 trials evaluated variations of a particular treatment approach, (different doses, isotopes or duration of RT); • 6 trials included men with locally advanced disease (24% of all patients); • Only some studies reported age, ethnicity, tumor stage, or Gleason score;

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	quality studies with long term FU (high); < 2 high quality studies or studies without long-term FU(medium); inconsistent results from studies of low quality or populations with little relevance to current practice/populations (low). • Evidence from nonrandomized trials, case series, and meta-analyses of same considered low strength; • Evaluated applicability of patient populations, clinical settings, length of FU, and adjustment for confounding.	• Most studies began enrollment before widespread PSA testing; • Erectile dysfunction occurred frequently after all treatments (RP, 58%; RT, 43%; androgen deprivation, 86%); • A higher risk score incorporating histologic grade, PSA level, and tumor stage was associated with increased risk for disease progression or recurrence regardless of treatment. **Conclusions:** *"Assessment of the comparative effectiveness and harms of localized prostate cancer treatments is difficult because of limitations in the evidence"*
Wilt (2008a)	See row immediately above.	
For recent brachytherapy studies, see entries following IQWiG (2007), below		
Chen (2009b)	**Cross-sectional** **QoL outcomes for RP, EBRT, and BT according to baseline function:** • Patients with untreated localized prostate cancer; • Metro-Boston hospitals, 1994-2000; • Baseline pre-treatment questionnaire (PCSI with FU at 3, 12, 24, 36 months); chart review to confirm demographics and clinical info.	**409 patients who chose RP, EBRT, BT:** • RP (127; 75 with NSRP); EBRT (190); BT (92); • All patients generally socio-economically advantaged; • RP patients younger (P<.001) and with fewer comorbid conditions (P<.003); • BT patients had lower risk disease than those receiving other treatments (P<.001); • Different levels of baseline sexual, bowel urinary function produced distinctive changes over 36 months: generally, average scale increases in dysfunction greatest among patients with normal baseline function; • Patients with normal and intermediate baseline sexual dysfunction had similar increases in dysfunction; • Patients with poor baseline urinary obstruction/irritation: average scales and level of function improved after treatment, especially with surgery. **Conclusions:** *"The use of functional levels to stratify treatment-related outcomes by pretreatment functional status and to display the proportions of patients with improved, stable, or worsened function after treatment provides information that more specifically conveys the expected impact of treatment to patients choosing among localized prostate cancer treatments."*
Johansson (2009)	**SPCG-4** **Cross-sectional analysis: QoL among men randomized to RP or watchful waiting:** • All living men included in Swedish component of trial between Jan 1989 and Feb 1996; • Data (by questionnaire at mean FU of 4.1 yr): specific symptoms; symptom-induced stress; sense of well-being; self-assessed QoL.	**376 men:** • Stratified by number of physical symptoms: anxiety or depressed mood less common, sense of well-being and QoL better throughout RP group than WW; • As number of physical symptoms increased: all psychological variables became worse and more prominent in WW group; • 6-8 yrs: significant (p = 0.03) decrease in QoL in WW group; • 24% of androgen-deprived WW patients reported high QoL vs. 60% of RP group. **Conclusions:** *"This paper indicates that watchful waiting may have its own psychological drawbacks in the subgroup of men whose disease progression warrants androgen deprivation. In making the choice between immediate treatment with surgery or watchful waiting, there is a need to determine QoL years gained or lost with each choice. We support concerted and continuing international effort*

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
		to build the clinical evidence base for prostate cancer treatment documentation of side-effects, and provision of support services. Additionally, we commend research to test decision aids to inform men of their choices based on QoL data."
Zhou (2009)	**Cross-sectional** **Comparison of RP, BT, EBRT, androgen deprivation, or no treatment:** • Men ≥65 with incident prostate cancer, 1999-2001; • Linked Ohio Cancer Incidence Surveillance System, Medicare, and death certificate files; • Overall and disease-specific survival differences among 5 therapies.	**10,179 men with incident cancers during study period:** • Disease specific survival at 7 yrs: localized, 92.3%; distant, 23.9%; • Controlling for age, co-morbidities, stage, Gleason in Cox multivariate regression: risk for prostate cancer death significantly reduced by RP or BT compared to no treatment; • Mono-therapy cohort: RP and BT associated with reduced HRs, 0.25 (CI, 0.13-0.48) ad 0.45(CI, 0.23-0.87) respectively; • Combination therapy cohort HRs: 0.40(0.17-0.94) and 0.64(0.27-0.80). **Conclusions:** *The present population-based study indicates that RP and BT are associated with improved survival. Further studies are warranted to improve clinical determinants in the selection of appropriate management of CaP and to improve predictive modeling for which patients may benefit most from definitive therapy vs. conservative management and/or observation."*
Bill-Axelson (2008)	**SPCG-4** **RCT: RP Vs WW at median 10.8 yrs FU (3 weeks-17.2 yrs):** • 695 men randomized 1989-1999; • FU complete through Dec 31, 2006; • Histopathologic review and blinded cause of death evaluation.	**RP(n = 347); WW (348):** • 137 deaths in RP group (47 due to prostate cancer); 156 in WW (68 prostate cancer); P = .09; • Difference in cumulative incidence of prostate cancer death stable after 10 yrs; • 12 years: 12.5% of RP group; 17.9% WW had died of prostate cancer; difference 5.4%; CI, 0.2-11.1; RR, 0.65 (CI, 0.45-0.95; P = 0.03); • Difference in cumulative incidence of metastases did not increase beyond 10 yrs; at 12 yrs: 19.3% of RP and 26% of WWs had distant metastases (difference 6.7%; CI, 0.2-13.2%); RR, 0.65 (CI, 0.47-0.88; P = .006); • RPs with extra-capsular growth had 14 times risk of prostate cancer death vs. those without it (RR, 14.3; CI, 3.3-61,9; P <.001). **Conclusions:** *"Radical prostatectomy reduces prostate cancer mortality and risk of metastases with little or no further increase in benefit 10 or more years after surgery."*
Sanda (2008)	**Cross-sectional** **QoL/satisfaction among survivors and spouses/partners:** • 9 US academic medical centers, March 2003-march 2006; • Men with previously untreated stageT1-2 and spouses or partners up to 24 months; • Primary treatment with RP, BT, EBRT;	**1201 patients; 625 spouses/partners:** • AHT associated with worse outcomes across multiple QoL domains for BT or EBRT; • BT: long-lasting urinary irritation, bowel, sexual symptoms; transient problems with vitality or hormonal function; • RP: adverse effects on sexual function mitigated by nerve-sparing procedure; urinary continence and obstruction improved, particularly in patients with large prostates; • No treatment-related deaths; • Serious adverse events rare; • Treatment-related symptoms exacerbated by obesity, large prostate size, high PSA, older age; • Black patients reported lower satisfaction with overall outcomes; • Changes in QoL significantly associated with satisfaction.

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
		Conclusions: *"Each prostate cancer treatment was associated with a distinct pattern of change in quality-of-life domains related to urinary, sexual, bowel, and hormonal function. These changes influenced satisfaction with treatment outcomes among patient and their spouses or partners."*
Wu (2008)	**Cross-sectional** **QoL after multimodal therapy in high-risk disease:** • CaPSURE database; national registry, 1995-; • Patients from 31 community, academic and government urology practices complete HRQol survey every 6 months after treatment with primary therapies (RP, ERBRT; BT with or without adjuvants);	**2204 men:** • RP, 1427; 267, EBRT; 510, BT%; • When ADT + RP, EBRT, or BT: transient loss of sexual function that improved over 9 months; • EBRT plus BT: continuous worsening of urinary function/bother over 21 months; **Conclusions:** *"Multimodal therapy may lead to declines in health related quality of life especially in the domains of urinary function, urinary bother and sexual function. These effects must be considered and patients counseled appropriately before initiation of multimodal therapy."*
IQWiG (2007)	**What are benefits and harms of low-dose-rate permanent interstitial brachytherapy in localized prostate cancer compared with standard surgical procedures, percutaneous radiotherapy, and watchful waiting?** **Patient-relevant therapy goals and substantially different types of brachytherapy:** • Multiple databases to June, 2006; • RCTs, non-randomized trials, and observational studies with concurrent controls provided adequate control for confounders reported; reporting overall survival, disease-free survival, symptoms, or QoL.	**11 studies (10,900 patients):** • No RCTs and only 4/11 were prospective; all with substantial methods limitations (lack of control for confounders, lack of of blinding, or different BT techniques); • Meta-analysis precluded by low quality of studies; • None compared BT to WW, investigated a combination of BT + other therapy, or compared different types of brachytherapy to each other; • Overall survival: no studies investigated overall survival or disease-specific mortality; no conclusions possible on relative advantages or disadvantages vs. other therapies for localized disease; all studies used PSA outcomes, but not survival. • No studies reported adverse events, number or duration of hospital stays, necessity and duration of catheterization, or FU required for post-treatment ED, urinary or rectal dysfunction. **Conclusions:** *"In patients with localized prostate cancer, indications exist (based on data from non-randomized observational studies) of an advantage of brachytherapy vs. radical prostatectomy) concerning impairment of sexual function and urinary incontinence. With regard to rectal function, this also applies to the comparison between brachytherapy and percutaneous radiotherapy.* *In respect of overall survival, as well as disease-specific and disease-free survival, no evidence is available to demonstrate a superiority or equivalence of brachytherapy versus prostatectomy or radiotherapy.* *Therefore, the potential advantages of brachytherapy with regard to organ function and quality of life in patients with localized prostate cancer as the only evidence are insufficient to apply this procedure, as potential harms regarding survival and disease-related symptoms cannot be excluded with absolute certainty. We therefore urgently recommend the conduct of sound clinical studies in order to define the relevance of brachytherapy compared with other treatment options."*
Butler (2009)	**Case-control:**	**55 biochemical failure cases due to rising PSA; 110 controls:**

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	• Biochemical failures among patients receiving brachytherapy (^{125}I or ^{103}P mono-therapy or with EBRT); 1994-March 2006 (cases); • 2/1 matching (for risk group, radionuclide and prescribed dose, time of implant) with non-failure patients (controls); • West Virginia cancer center; • Dose volume histogram (DVH) calculated for all subjects; • Median FU, 10.9 years;	• Only GS significantly different, cases vs. controls; • Stratified by radionuclide and approach: 72.7% of ^{125}I patients had monotherapy, 15.9% of ^{103}P; • No significant differences between cases and controls for any dosimetric or radiobiologic variable for either therapy type. **Conclusions:** *"…there were no radiobiological parameters derived for detailed DVH-based analysis that predicted for biochemical control. This may indicate that in our approach, implant dosimetry is at or near the limits of clinically effective dose escalation."*
Morris (2009)	**Cross-sectional** **Brachytherapy outcomes for low- and intermediate-risk:** • Provincial urologic research registry in British Columbia (Canada); • Consecutive procedures: July 1998 - October 2003; • Low risk (GS ≤ 6; pretreatment PSA≤ 10 ng/ml; unilateral disease) and "low-tier" intermediate risk (organ-confined; GS 7 and/or PSA 10-15); • 2 patients included on ITT basis because brachytherapy aborted for anatomic reasons and received EBRT; no others received supplemental EBRT; • ADT 3 months before and 3 after part of protocol. • FU at 6 weeks, 6 months for 2-3 yrs, then annually.	**1006 patients:** • 585 (58%; low-risk); 419 (42%; intermediate); 657 received ADT; • 80% of those receiving ADT had adequate FU to assess testosterone recovery: 94.4% recovered to ≥ 5nmol/L at median time 9.6 months after ADT completion; • Median FU: 54 months (biochemical); 66 months (survival). **Biochemical outcomes:** • 35 biochemical recurrences: 3/35 with PSA profiles more typical of benign increase; • additional 22: benign increase in PSA that returned to <0.5ng/mL without intervention; • Overall 5-yr bNED: 95.6% ±1.6% CI; 7-yr 94%±2.2%; • Univariate analyses: no pretreatment or dosimetric variables were associated with bNED; • Median nadir PSA: 0.05ng/ml (<0.01-4,8); • 616 patients bNED at ≥4 yrs (median 62 months): median PSA was 0.04ng/ml (mean 0.1) at last FU. **Metastases and survival:** • 5- yr actuarial freedom from distant metastases; 99.1%±0.6; • Disease specific survival: 5 and 7 yr: 99.8%±0.2%; • Overall survival: 5-yr, 95.2%±1.4%; 7-yr, 93.4%±1.8%; • 30-day mortality: nil (survival range 31-8.75 yrs). **Conclusions:** *"When consistently planned and delivered, low-dose-rate brachytherapy, without supplemental external beam radiotherapy or intra-operative planning, can produce cancer-specific outcomes for men with low- and "low tier" intermediate-risk prostate cancer at least equal to that produced by external beam radiotherapy or surgical prostatectomy."*
Shapiro (2009)	**Cross-sectional** **Long-term BT outcomes in younger men:** • Patients with T1-2, N0, M0 disease, treated 1992-2005 in urban US hospital; • BT with or without HT, with or without EBRT, or all three; • Multivariate analyses for impact of age < 60, other clinical variables;	**2119 patients:** • 237 (11%) < 60 at diagnosis; • Overall freedom from progression: 90.1% (5 yrs); 85.6% (10 yrs); • Overall multivariate analyses: PSA ($p<0.01$); GS ($p<0.0001$); year of treatment ($p<0.001$) were associated with freedom from progression; but age< 60 ($p = 0.95$) and clinical stage ($p = 0.11$) were not;

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	• Kaplan-Meier calculations for disease progression; • Median FU, 56.1 months.	• Younger cohort: 10-yr freedom from progression: low risk (91.3%); intermediate (80.0%); and high risk (70.2%) versus 91.8%, 83.4%, 72.1% in patients > 60; • Adverse event rates from previous studies only reported by these authors, not from their own series. **Conclusions:** *"Our long-term results confirm favorable outcomes after permanent prostate brachytherapy in men younger than 60 years. Outcomes are impacted by disease related risk factors but not by age or clinical stage. Definitive treatment options for younger men with clinically localized prostate cancer should include permanent prostate brachytherapy."*
Cosset (2008)	**Cross-sectional** **Overall and relapse-free survival in a series including ABS higher-risk patients:** • Jan 1999-Sept 2004; • Urban hospital/research institute in Paris; • Most met ABS criteria; 34% higher risk (PSA 10-15 or GS 7); • ^{125}I brachytherapy; clinical staging and assessment by endo-rectal MRI; • Mean FU, 43 months (1-86).	**Total 809 patients:** • 533 (69.9%) met all ABS monotherapy criteria (Stage T1-t2A; GS 2-6; PSA <10mg.ml); 276 (34.1%) did not; • Non-ABS group: 150 met criteria except for PSA 10-15; 100 with GS 7; 26 both; • Borderline difference between groups for age (p = 0.04), lower in ABS group; • Significant difference (p< 0.001) between groups for tumor extension/percent T2 patients higher in non-ABS group; • Overall 5-yr survival: 98; NS difference ABS Vs non-ABS (p = 0.62); • 5-yr relapse free survival: significantly lower in non-ABS (p = 0.001) but still satisfactory at 94%; • Subgroup analyses: better results in patients with PSA 10-15 than GS. **Conclusions:** *"Our results suggest that selected patients in the intermediate-risk group of localized prostate cancers can be safely proposed as recipients of permanent implant brachytherapy as monotherapy."*
Keyes (2009)	**Cross-sectional** **Predictive factors for acute and late urinary toxicity:** • Case series: consecutive patients; • 4 Brachytherapy Program clinics for British Columbia (Canada) Cancer Agency, 1998-2003; • Data: baseline PSA and testosterone; toxicity scales; • Patients excluded from this analysis: patients treated during first year; death with < 34 months FU; living in remote areas.	**712 patients:** • Median FU, 57 months; • IPSS returned to baseline at median 12.6 months; • Patients with high baseline IPSS had quicker resolution; • Multivariate analyses for slow IPSS resolution: high baseline IPSS; higher D90 (dose covering 90% of prostate); maximal post-implant IPSS; urinary retention; • Actuarial 5-yr late (> 12months) RTOG grade 0, 1, 2, 3, 4 toxicity: 32%, 36%, 24%, 6.2%, 0.1% respectively; 7-yr prevalence grade 0-1, 92.5%; • Multivariate analyses for late higher grade toxicity: higher baseline and post-implant IPSS, acute toxicity, higher volume covered by 150% of dose; • More recently performed procedures has less acute toxicity and patients receiving hormonal therapy had less late toxicity (p<0.02). **Conclusions:** *"Most urinary symptoms resolved within 12 months after prostate brachytherapy, and significant long-term toxicity was very low. Refined patient selection and greater technical expertise in brachytherapy were associated with less toxicity."*

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Fang (2008)	**Cross-sectional** **GI, GU toxicity for HDRBT plus EBRT vs. EBRT alone:** • 88 consecutive patients with T1c-T3b cancers received EBRT alone; 55, HDRBT +EBRT; • Academic medical center in Taiwan • Median dose: EBRT alone, 70.2 Gy; HDRBT +EBRT, 50.4Gy (HDRBT 2-3 weeks before EBRT, then 12.6 Gy oin 3 fractions over 24 hrs).	**Biochemical relapse:** • 25.2% of EBRT alone patients; • 12.7% of combination patients. **5-yr actuarial biochemical relapse free survival:** • EBRT alone, 65%; • Combination, 66.7%; (P = 0.76). **5-yr late Grade 2 or 3 GI toxicity:** • 62.8%, EBRT alone; • 7.7%, combination (P<0.01); • Multivariate analyses: only predictor for late GI toxicity was mode of RT. **Late GU toxicity:** • EBRT alone, > grade 2: 14.8% (P= 0.86); • Combination,> grade 3: 15.9%; 21.9% (P = 0.40). **Conclusions:** *"The addition of HDTBT before EBRT with a reduced dose from the EBRT produces a comparable survival outcome and GU toxicity but significantly less GI toxicity.*
Mitchell (2008)	**Cross-sectional** **Multi-institution brachytherapy registry:** • 3 UK urban hospitals; • All patients receiving I^{125}, 2003-2006; • Biochemical failure and adverse effects.	**1535 patients:** • Patient and tumor characteristics similar across centers; • 15% received NHT; • IPSS increased from baseline to 18 and 6 weeks, then not NS different from baseline by 12 months; • 9% required catheterization for median 53 days, but strictures at end of FU in 1%; • Actuarial bNED: 94.4% or 94.5% at 5 yrs, according to definition used; **Conclusions:** *"This ongoing collaboration shows that with limited infrastructure (a single industry-sponsored data manager), a large multi-institutional database estimated to represent one-third of implants carried out in the UK during this time can be developed. Patient selection was similar across all centers and adhered to published guidelines. Early biochemical and toxicity outcomes confirm the efficacy and tolerability of I^{125} prostate brachytherapy in a large cohort of patients. A further analysis is planned."*
Merrick (2008)	**Case series** **Outcomes of brachytherapy in men ≥75 yrs:** • Clinically staged cases performed by one radiation oncologist at multiple US hospitals, 1995-2004; • Brachytherapy with or without supplemental therapies; • Cancer sp3ecific survival, overall survival, biochemical progression free survival (PSA≤0.40 ng/ml after nadir.	**145 patients ≥75:** • 9-yr outcomes: cancer specific survival, 99.3%; bPFS, 97.1%; Overall, 64.5%; • Median FU, 5.8 yrs; • 37 patients died: 83.% due to cardiovascular disease or second malignancies; 1 patient (0.7%) of metastatic prostate cancer; • No clinical features predicted overall survival; overall survival, bPFS, non-cancer deaths predicted by tobacco use.

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		Conclusions: *"After brachytherapy, high rates of CSS and bPFS are noted in elderly cancer patients. Overall, approximately 65% of patients are alive at 9 years, with survival most closely related to tobacco status. We believe our results support an aggressive locoregional approach in appropriately selected elderly patients."*
Schäfer (2008)	**Cross-sectional:** **Long-term QoL after brachytherapy:** • One academic medical center in Germany, 1998-2003; • Prostate-specific QoL instrument, PSA, GS and/or grading.	**296 men:** • Group 1 (< 65 yrs); Group 2 (≥ 65); • 238 returned QoL questionnaires at median FU 51 months: 77.8% of group 1; 73.4% of 2 in very good or excellent state of health with low risk, of moderate (10.4%) or strong (1.0%) symptoms for urinary function; • Stress incontinence uncommon; • 28.2% reported moderate or strong sexual function symptoms; • 48.6% (Group1) and 2.25% (2) reported no or minor erectile dysfunction; • No severe or overall rectal dysfunction (<2%). **Conclusions:** *"Our data substantiate the favorable long-term HRQoL outcomes associated with modern PB techniques. Significant age differences were observed in sexual symptoms and less pronounced age differences in urinary symptoms. We found a low rate of urinary symptoms and no evidence of severe rectal dysfunction."*
Shelley (2007)	**Cochrane review** **Relative clinical and economic benefits of cryotherapy vs. standard treatments:** • Multiple databases, 1996-2006; • RCTs, quasi-randomized, or controlled trials comparing cryotherapy to RP, EBRT or active surveillance as primary treatment for men with localized prostate cancer (stage T1-T3); • Outcomes: biochemical disease-free survival; treatment induced complications; disease-specific survival; overall survival; QoL; economic impact.	**No RCTs compared cryotherapy to other therapies for primary treatment of localized prostate cancer:** • All available studies were case series: reviewed if cryotherapy was performed using TRUS and urethral warming in ≥ 50 patients with localized cancer and reported ≥1 yr FU; • 8 case series met criteria, 2 of which were retrospective: • 1483 patients overall: mean age 41-84; T1, 0-43%; T2, 24-88%; T3, 1-41%; T4, 0-14%; mean PSA, 9.7-39ng/mL; Gleason <7, 6-37%; • One additional study compared cryotherapy (total and standard with urethral preservation) to RP: success (post-treatment PSA of 0.2 mg/m) in 94% of patients for standard cryotherapy, 73% for RP; other studies used thermocouples to monitor temperature during procedure: overall survival sat 5 yrs, 71-89%;1.4-13% had positive post- treatment biopsy; • Major complications in all studies: impotence (47-100%); incontinence (1.3-19%); urethral sloughing (3.9-85%); fistula (0-2%); bladder neck obstruction (2-55%); stricture (2.2-17%); and pain (0.4-3.1%); • Most patients sent home following day (1-4 days). **Conclusions:** *"Cryotherapy offers a potential alternative to standard therapies for the primary treatment of localized prostate cancer. However the poor quality of the available studies makes it difficult to determine the relative benefits of this modality. Randomized trials are needed to fully evaluate the full potential of cryotherapy in men with this disease. Patients selecting cryotherapy as*

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		their therapeutic option should be made fully aware of the reported efficacy, complications and the low-grade evidence from which these data are derived."
Ferrer (2008)	**<u>To assess available comparative evidence on treatments for localized prostate cancer:</u>** • Systematic review (Spanish with English abstract); 3-yr FU on 770 patients treated in outpatient departments of 10 Spanish hospitals; • Interventions: RT, BT, EBRT.	**770 Spanish patients:** 71 RP; 112 EBRT; 162 BT: • NS differences among treatments at 3 years by generic QoL questionnaires, although RP had adverse effect on sexual function that persisted for 3 yrs; • Mean scores on prostate symptoms instruments: RP, 33.2; EBRT, 42.9; BT ($p<0.001$); **Conclusions:** *"Prostatectomy has a marked negative impact on sexual function, while by the third year patients treated with external radiotherapy or brachytherapy had recovered similar levels of function to those previous to the treatment."* **Recommendations:** *"Methodologically solid randomized clinical trials with sufficient sample size and follow-up periods are necessary. Given the differences among side effects with surgery and radiotherapy, it is important that the patient participates in choice of treatment according to his values and preferences."*
NICE (May 2006b)	**<u>Summary of guidance and supporting evidence:</u>** **High dose rate brachytherapy in combination with external-beam radiotherapy:** Methods details in row below • Multiple databases, 1966-2005; • Included: English-language good-quality studies; other languages only where added substantively to knowledge base; • Excluded: no clinical outcomes reported; narrative review, laboratory or animal study.	**Efficacy:** • Matched case series: actuarial 5-year survival better for combination that EBRT alone (86% vs. 54%'; $p<0.001$); • Analysis across 3 case series: 5-yr survival rates for combination: 85%, 79%, 93%; • Series of 611: 10-yr survival of 65%. **Guidance:** *"Current evidence on the safety and efficacy of high dose rate (HDR) brachytherapy in combination with external-beam radiotherapy for localized prostate cancer appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.* *A multidisciplinary team should be involved in the planning and use of this procedure."*
NICE(January 2006a)	**High dose rate brachytherapy for localized prostate cancer:** • Multiple databases, 1966-2005; • Included: English-language good-quality studies; other languages only where added substantively to knowledge base; • Excluded: no clinical outcomes reported; narrative review, laboratory or animal study.	**2 non-randomized controlled studies, 6 case series in 7 reports:** **Efficacy:** • 5-yr actuarial survival with HD BT+EBRT as in row above; 10 yr, 65%; 7.2 yrs, 84%; • Biochemical control+ EBRT: 5 yrs, 67%; 3 yrs, 98% high dose BT; 97%, low dose; • Analyzed by risk factors (PSA, Gleason, stage): 5-yr biochemical control less frequent in high risk ($p<0.0001$); • Case series: no viable cancer on biopsy in 86%; **Safety:** • Men who were potent at baseline: 14% impotence at 5 yrs; 30% at 3 months; 54% at 3 years; 76% at 7 yrs;

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		• Urethral stricture: 1.5-8%; • Urinary-retention free survival: 86% at 5 yrs. Guidance in row above.
NICE (July 2005b)	**<u>Evidence overview</u>** **Low dose rate brachytherapy for localized prostate cancer:** • Multiple databases, 2002-2004; without language restriction; • Included: English-language good-quality clinical studies; other languages only where added substantively to knowledge base; • Excluded: no clinical outcomes reported; narrative review, laboratory or animal study; • Outcomes: PSA relapse free survival; disease-free survival; overall survival; QoL; safety (short- or long-term GI or GU toxicity; sexual function).	**Effectiveness: "***Evaluation of the effectiveness of brachytherapy is hampered by the diversity of different techniques used, patient population selection criteria (clinical stage, Gleason score, pretreatment serum PSA), use of adjuvant therapies such as external beam radiation and androgen deprivation therapy, and different lengths of follow-up. Despite a very large literature base identified at the outset, few studies met the inclusion criteria for this review and the majority of these were case series of varying quality.* *Studies reporting outcomes over 5 years are rare and the majority of studies use proxies for disease free survival based on serum PSA measurements. Comparisons between brachytherapy and standard treatments are rare and find little difference in outcomes."* **Safety:** *"The evidence in terms of complications is mixed. Existing systematic reviews suggest that brachytherapy results in rates of complications similar to or lower than standard treatments. The rates of complications reported in these reviews were similar to the level 5 primary studies (descriptive case series) presented in the current review. However two matched case-control series suggest that disease-specific QoL is lower among brachytherapy patients than patients receiving external beam radiation alone, or when compared with a healthy population. General HRQoL has been shown to be comparable in brachytherapy to standard treatments and similar to age-matched controls. Impotence rates for brachytherapy appear to be better than rates of 50% reported for radical prostatectomy."*
NICE (2005a)	**<u>Evidence overview</u>** **High-intensity focused ultrasound for prostate cancer:** • Multiple database, 1966-Feb 2004; no language restrictions • Good quality clinical studies; • Excluded: no clinical outcomes reported; animal studies; narrative reviews.	**Efficacy:** • The evidence was based on case series and the main outcomes reported were negative biopsy rates and PSA nadir levels; • Some studies reported disease-free survival rates but the criteria used to define disease varied; • A systematic review, including eight case series, reported a negative biopsy rate of 60% (37/62) in one study with follow up not specified and 80% (75/95) in a study with 3-year follow up; • In further studies in the review, the proportion of patients without clinical or biochemical evidence of disease ranged from 56% (28/50) to 66% (67/102) at 19 months; • Three additional case series reported negative biopsy rates between 87% (251/288) in a study with mean follow-up of 13 months and 93% (128/137) in a study with mean follow up of 22.5 months; • One of these studies, which included 146 patients, also reported disease-free survival rates of 54% or 71.5%, depending on the criteria used to define disease-free status; • The specialist advisors considered that long-term data are needed to establish whether the procedure reduces prostate-cancer-specific mortality. **Safety:**

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		• Urinary tract infections and stress incontinence were the most commonly reported complications, in 4% (6/137) to 48% (46/96) and 8% (9/111) to 23% (23/102) respectively; • Recto-urethral fistula in 0.7% (1/137) and 2.6% (3/111); • Impotence in 25% (75/315) and 100% (62/62), but men who were potent before treatment rarely reported; • Other complications: prolonged urinary retention; urge incontinence; urgency; bladder neck stenosis; urethritis; prostate abscess; epididymitis; asymptomatic rectal burns; chronic pelvic pain. **Guidance:** *"Current evidence on the safety and efficacy of HIFU, as measured by reduction in PSA levels and biopsy findings appears adequate to support the use of this procedure for the treatment of prostate cancer provide that the normal arrangements are in place for consent, audit and clinical governance.* *The effects of HIFU on prostate cancer quality of life sand long-term survival remain uncertain. Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options.* *Interpretation of the data was difficult because it was not clear from the literature when the procedure was used for primary or for salvage treatment. Further research and audit should address clinical outcomes, long-term survival and indications for treatment (differentiating between use of the procedure for primary and for salvage treatment.)"*
Alibhai (2004)	Medline, 1966-March 2003: • English-language RCTs of RP, EBRT, BT, WW, or androgen deprivation in localized prostate cancer; • Inclusion: patients randomized to treatment; at least two primary therapeutic modalities compared; • Excluded: evaluations of neo-adjuvant or adjuvant hormonal therapy; but no exclusions on methods quality criteria reported.	**9 articles representing 4 separate trials:** • VACURG (3 studies):1, RP + 5 mg DES daily vs. RP + placebo; at median FU 13 yrs, NS difference between groups but excess cardiovascular deaths with DES; VACURG 2, &3,142 patients with T1a-b or T2 randomized to RP vs. WW; treatment received analysis of 111 patients, 43 (5 due to prostate cancer) died during FU; no difference in survival or time to death adjusted for age and grade; but RP group developed more (NS) metastases; • UROG trial: 106 patients randomized to RP vs. EBRT; differences in progression rates between groups significant at 5 yrs and 20 months in favor of RP; • Japanese trial: 95 patients with locally advanced disease randomized to RP or EBRT: progression free survival and disease-specific survival at 5 years significantly better for RP; • Scandinavian trial: 675 patients (T1a-b or T2; moderately or well differentiated) randomized to RP vs. WW: at median 6.2 yrs FU, disease-specific mortality better for RP. **Conclusions:** *"There is high-quality evidence from one randomized trial in favor of surgery over watchful waiting with palliative intent for non-high grade localized prostate cancer. However, most tumors in this study were clinically diagnosed rather than screen-detected. Further randomized trials examining the treatment of screen-detected localized prostate cancer are needed; several are currently under way."*
NICE (2004)	**Evidence overview** **High-intensity focused ultrasound:** • Multiple databases, 1966-2004;	**This review relied on single existing systematic review (Hummel, 2003; below):** **Hummel:** insufficient evidence to draw conclusions regarding effectiveness of HIFU.

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	• English-language good-quality clinical studies reporting "information relevant to safety and/or efficacy of HIFU" in patients with prostate cancer; other languages only where added substantively to knowledge base; • Excluded: no clinical outcomes reported; narrative review, laboratory or animal study.	
Hummel (2003)	**Clinical and cost-effectiveness of new and emerging technologies for early localized prostate cancer:** • Interventions covered: NHT; AHT; BT; 3D-CRT; IMRT; cryotherapy; • Multiple databases, -2002; "all literature relating to these interventions" (survival, QoL, adverse events) without language or study/publication type restrictions.	**104 studies evaluating 12 interventions:** • 13 RCTs for NHT: no evidence of benefit in bNED survival; • AHT: 1 RCT and 3 case series indicating no overall survival benefit except conflicting evidence for higher risk patients; • Largest number of studies for BT: mostly descriptive case series suggesting brachytherapy may be more effective (biochemical DFS) than standard treatments for lower risk patients but less effective for intermediate- or higher-risk; evidence for complications mixed; • 3D-CRT: significantly fewer GI complications than standard radiotherapy. **Conclusions:** *"Very few RCTs were identified, with the majority of included studies being descriptive case series, open to patient selection bias and measuring surrogate end points with short-term follow –up. It is difficult therefore to draw conclusions on the relative benefits or otherwise of the newer technologies owing to the lack of substantive evidence of any quality and the lack of comparisons between the newer technologies and with standard treatments."*
CCOHTA (2002)	**Brachytherapy for prostate cancer** Pre-assessment with limited search • PubMed and Cochrane databases; • Included: studies published or in progress, relating to prostate brachytherapy;	**9 HTAs and systematic reviews completed or in progress** **Overall summary:** • No RCTs available • Insufficient evidence of effectiveness, cost-effectiveness, risks, benefits or adverse events of brachytherapy relative to alternative therapies
Crook (2001)	**Brachytherapy in clinically localized prostate cancer:** • Systematic review plus consensus; • Multiple databases, 1988-99; • Included: full-text CPGs, systematic reviews, RCTs, controlled trials in patients with T1 or T2 cancer; procedure performed under ultrasound or CT guidance; outcomes reported as freedom from biochemical failure, biopsy results or toxicity.	**No RCTs available** • 13 case series and 3 cohort studies; • Rates of freedom from biochemical failure varied with tumor stage, grade and pretreatment PSA levels: T1 or T2, Gleason < 6. PSA ≤10ng (µg/L) comparable to patients having RP; • Acute urinary retention in 1-14% of patients; • Long term sequelae: <5% of patients (urinary incontinence, cystitis, urethral stricture, proctitis); • 86-96% of patients retained potency. **Conclusions:** *"At present there is insufficient evidence to recommend the use of brachytherapy over current standard therapy for localized prostate cancer. Brachytherapy using transrectal ultrasound guidance for seed implantation is promising in terms of freedom from biochemical failure in selected patients with early-stage prostate cancer. Brachytherapy is currently available outside of clinical trials, but whenever possible patients should be asked to participate in randomized trials comparing brachytherapy and current standard therapy. Brachytherapy should be available to selected patients*

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		(those with T1c or T2a tumors, a Gleason score of 6 or lower and a serum PSA of 10µg/L or less), after discussion of the available data and potential adverse effects."
SBU (2000):Alert	**Early assessment document, not completely reported systematic review:** • 4 point scale for evidence:1, good; 2, moderate; 3, poor; 4, no evidence available;	**Only uncontrolled observational studies available:** • Poor scientific evidence concerning patient benefits, short-term effects, and risks of the method; • No evidence regarding cost-effectiveness or longer-term effects. **Conclusions:** *"Since there is no evidence to show that brachytherapy is superior to other treatment or to no treatment in managing clinically localized prostate cancer, the method should be used only within the framework of controlled clinical studies until further evidence becomes available."*
Other review topics		
Sutcliffe (2009)	**NHS HTA Program Assessment** **Novel prognostic markers to distinguish men with indolent vVs. fast-growing prostate cancer:** • Multiple databases, March-April 2007; • all references relating to novel biomarkers or prognostic models" for men with early localized prostate cancer (T1-T3N0M0 or Jewett-Whitmore stages A, B, C before or at treatment; minimum sample of 200; mean FU 5 years; • End points/outcomes: overall survival; disease-specific survival; disease-free survival biochemical (PSA) freedom from recurrence; clinical recurrence.	**30 papers:** • 28 concerned with novel biomarkers, 5 with prognostic models; 3 with both; • 21 novel biomarkers identified: variability of results, poor quality of studies, lack of studies for some categories of marker make clear conclusions difficult and preclude quantitative synthesis. **Promising:** acid phosphatase level; non-classical use of Gleason score; PSA kinetics (velocity or doubling time); % positive biopsy cores. **Not promising:** β-catenin expression; creatinine; germ-line genetic variation in vitamin D receptor; tumor dimension/size. **Inconclusive:** % cancer in surgical specimen; androgen receptor: CAG repeats; DNA ploidy; CYP3A4 genotypes; Ki67 LI; Bcl-2; p53; syndecan-1;CD10' stat5 activation status. **Conclusions:** *"The main sources of uncertainty for the results of the novel prognostic marker review were the heterogeneity between studies, the small number of studies and the poor quality of studies, which made it difficult to reach firm conclusions on the prognostic value of novel markers. Similar issues, as well as lack of external validation and lack of a well-established measure of performance for prognostic models, affected the conclusions that could be reached on the prognostic models. The poor evidence is a key finding of this review. Other reviews of prognostic markers and models have also highlighted this problem."*
Vickers (2009)	**Value of PSA dynamics (velocity and doubling time) as prognostic markers:** • Medline –Feb 2007; • "Articles on PSA dynamics and prostate cancer" reporting pretreatment PSA in patients with intact prostate at time of final measurement required for dynamics calculation and including at least one endpoint (diagnosis of cancer, stage or grade, biochemical recurrence after treatment or	**87 eligible studies:** • 17 for doubling time, 64 velocity, 6 both; • 5 studies used idiosyncratic definition of dynamics in addition to velocity or doubling; • Median number of patients, 295 (inter-quartile range, 86-1095); • Vote count: 47 articles (54%) reported positive results; 30 (34%) negative; 10 (11%) unclear; • No significant relationship between statistical methods used and reporting of positive vs. negative results (P>.2); • Only one model incorporated both PSA alone and a dynamic, so review included studies

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	progression for active surveillance. Metastases or death from prostate cancer); at least two measures of PSA before a clearly defined point in patient's history; • Quality assessment: reporting of statistical significance or predictive accuracy of model including PSA dynamics.	comparing accuracy: generally, such studies found PSA alone to be more accurate than dynamic, trivial differences between dynamics, or had serious methodologic shortcomings (verification bias or small samples). **Conclusions:** *"There is little evidence that calculation of PSA velocity or doubling time in untreated patients provides predictive information beyond that provided by PSA alone. We see no justification for the use of PSA dynamics in clinical decision making before treatment in early-stage prostate cancer."*
Wolters (2009)	**ERSPC Rotterdam** **PSAV as predictor for significant cancer in cases detected by screening: cross-sectional analysis of men in screening arm:** • Does PSAV reduce unnecessary biopsies or detection of indolent disease? • First and second screening rounds: PSA > 3.0 ng/ml initiated biopsy with classification as benign, possibly indolent, or clinically significant	**Biopsies in 2217 men:** • 441 cancers: 333 clinically significant; 108 possibly indolent; • Use of absolute PSAV cut values reduced biopsies but also led to significant numbers of missed indolent and significant disease; • PSAV predicted disease (OR, 1.28, p <.001) and clinically significant disease (OR 1.46; p<0.001) in univariate analysis; • Multivariate analysis (age, PSA, DRE, TRUS outcome, previous biopsy): PSAV NS predictor of cancer (OR 1.01, p = 0.91 or significant cancer (OR 0.87, p= 0.30). **Conclusions:** *"The use of PSAV as a biopsy indicator would miss a large number of clinically significant cancers with increasing cut-offs. In this study, PSAV was not an independent predictor of a positive biopsy in general or clinically significant disease on biopsy. Therefore PSAV, does not improve the ERSPC screening algorithm."*
Hövels (2008)	**To compare accuracy of CT and MRI in diagnosis of pelvic node metastases in prostate cancer:** • Medline and Cochrane, 1980-2003; • Included: English-language diagnostic accuracy studies (CT or MRI); patients with prostate cancer diagnosis; histopathology as gold standard; Se, Sp, PPV, NPV reported or could be calculated; • Quality assessment: sample size; subject enrollment procedure; reference tests; blinding of test interpreters; clear description of tests.	**24 articles:** 4 compared MRI to CT and were considered as 2 separate studies in review); • 10 MRI studies (628 patients); 18 CT (1024) used in meta-analysis; • Pooled diagnostic accuracy: Se for CT, 0.42 (CI, -.2-0.56); MRI, 0.39 (CI, -.19-0.56); Sp for CT, 0.82(CI, 0.9-0.83); MRI, 0.382 (CI, 0.79-0.83); • Study quality: only one study described patients in detail; 10/28 studies reported average Gleason or PSA. **Conclusions:** *"CT and MRI demonstrate an equally poor performance in the detection of lymph node metastases from prostate cancer. Reliance on either CT or MRI will misrepresent the patient's true status regarding nodal metastases and thus misdirect the therapeutic strategies offered to the patient."*
Miles (2007)	**Cochrane review** **RCTs of any interventions for SD following cancer treatment:** • Multiple databases, 1966-2007; • RCTs enrolling patients >16 who had previously received treatment for any cancer without language restrictions; • Interventions: any intervention for SD that occurred as a	**11 RCTS with 1743 participants:** • Quality of trials was poor: • 10 trials for SD in men following prostate cancer treatment; 1 trial in women (lubricating vaginal cream following treatment for cervical cancer); • 4 trials of phospho-diesterase inhibitors in men significantly favored treatment group; • Negative effects few and usually mild to moderate headaches or flushing; one trial reported 6 tachycardia events and 6 chest pain.

Citation	Objective/Methods	Results, Conclusions, Recommendations, Comments
	result of treatment for cancer (psychological, pharmacological, mechanical or CAM) and whose primary aim was to ameliorate SD arising as a direct result of cancer treatment; interventions compared with control, placebo, usual care, or observation; • Outcomes: proportion of individuals showing improved sexual function; scores on standardized sexual function scales; adverse or side effects; number of participants dropping out; • Exclusions: observational studies; RCTs evaluating preventive measures (nerve-sparing surgical techniques, breast reconstruction, or avoidance of one particular therapy); studies including volunteers reporting SD.	**Conclusions: "***PDE5 inhibitors are effective treatments for SD secondary to treatments for prostate cancer. Other interventions identified need to be tested in further RCTs. The SD interventions in this review are not representative of the range available for men and women. Further evaluations are needed for these interventions for SD following cancer treatments."*
Schröder (2008)	**<u>Models for predicting risk of positive biopsy versus PSA alone:</u>** • ANNs or nomograms; • Multiple databases -July 2007; manual searches of reference lists; • Included: use of assessment instrument to examine risk of positive biopsy in men without known cancer diagnosis; intra-model comparisons with PSA alone; inter-model comparisons (AUC from ROC curve); individual case examples as comparisons.	**23 studies examining 36 models:** • With exception of 2 studies, all models had AUC ≥7.0, 8 had ≥8.0, 4 ≥0.85; • Variable validation status; • 14 models compared AUC to PSA alone: all showed benefit of AUCs (0.02-0.26); • 16 external validation comparisons: 13/16 AUC lower in general population than in model population; **Conclusions:** *"Nomograms and ANNs produce improvements in AUC over measurement of PSA levels alone, but many lack external validation. Where this is available, the benefits are often diminished, although remain significantly better than with PSA levels alone. In men without additional risk factors, PSA cutoff values alone provide a relatively precise risk estimate, but if additional risk factors are known, PSA values alone are less accurate."*
Cooperberg (2009)	**<u>Cancer of the Prostate Strategic Urologic Research Endeavor registry</u>** • Accuracy of CAPRA score (developed for RP) to predict metastases, prostate cancer-specific mortality, all-cause mortality for other treatments; • CaPSURE registry: Men with biopsy-proven disease reported by 40 primarily community-based urology practices across US; • Patients treated according to physicians' usual practices, then followed to death or withdrawal from study; • Direct medical records and death certificate confirmation of clinical and outcomes data.	**10,627 men:** • Treatments received: RP (5378); cryotherapy (425); BT (1441): EBRT (1262); ADT (1457); WW (664); • 311 (2.9%) developed bone metastases 251(2.4%) died of prostate cancer; 1582 (14%) of other causes; • Each single-point increase in CAPRA was associated with increased bone metastases (HR, 1.47; CI, 1.39-1.56); cancer-specific death (HR, 1.39; CI, 1.10-1.16); and all-cause death (HR, 1.13; CI, 1.31-1.48); • CAPRA was accurate for predicting metastases (c-index = 0.78); prostate cancer death (0.80); and all-cause (0.71). **Conclusions:** *"In a large cohort of patients with clinically localized prostate cancer who were managed with one of five primary modalities, the CAPRA score predicted clinical prostate cancer endpoints with good accuracy. These results support the value of the CAPRA score as a risk assessment and stratification tool for both research studies and clinical practice."*

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Nguyen (2009)	**<u>"Metagram"/catalog of available prediction tools</u>** **Categorized in table cells by treatment and outcome:** • Medline, 1950-2008; • "all published prostate cancer prediction tools" (nomograms, risk groupings, probability tables, ANNs); • Data extracted: derivation cohort characteristics; treatment including adjuvant therapies; outcome; prediction accuracy; validation status; for RP, only models based on pre-operative variables; • Metagram constructed using 16 localized disease treatment regimens and 10 outcomes to populate table cells.	**44 unique prostate cancer prediction tools:** • Assessed at least one of the 160 treatment/outcome cells to populate 31/160 cells; • Majority of tools assessed cancer control with biochemical control most frequent and survival less commonly reported; morbidity and QoL only reported by 3 tools; LOS and convalescence by none; • 17/31 populated cells contained multiple tools but for only one was direct comparison of predictive accuracy possible. **Conclusions:** *"Patients with clinically localized prostate cancer require our best estimates of treatment success and complications to make informed management decisions. Prediction tools are superior to physician judgment in this regard, but the sheer number of currently available tools, combined with a lack of head-to-head comparison data, creates a dilemma for the physician seeking an appropriate and reliable tool for patient counseling…a metagram that incorporates all currently available prediction tools for use in localized prostate cancer and has the potential to generate evidence-based and individualized risk estimates in a manner that is easily interpreted by the average patient. However, with only 31 of 160 cells in our metagram populated, there is a great need for additional models as well as improvements in the accuracy of existing tools."*
van den Bergh (2008)	**<u>Comparison of web-based risk calculators</u>** **PCPT vs. ERSPC:** • PSA range 02.-30ng/ml: prediction curves for virtual patients in both studies/using respective prediction models plotted; • Other data added: prostate volume; DRE; TRUS; previous negative biopsy; family history.	**Full results tabulated and presented graphically in article:** • Probability of finding cancer at sextant biopsy: PSA 4.0ng/ml: 26-64% by PCPT calculator; 73% ERSPC; • Important differences in derivation populations cause essential discrepancies between calculators: PCPT had few biopsies in higher PSA ranges; ERSPC had few in lower ranges; both calculators incorporated variables not available in the other; • TRUS and prostate volume have larger effects on predictions in comparable PSA ranges than race, age, family history, or previous biopsy. **Conclusions:** *"Before using risk calculators, uses must consider the underlying populations and what are the included or unavailable risk factors, and compare these to the patient. When these prerequisites are disregarded, dissimilarities will result in grossly inaccurate predictions for individual patients."*
Chun (2008)	**Nomogram development:** • 1132 evaluable men with biopsy confirmed localized cancer: consecutively referred for/received RP; • January 1992- June 2003; • Academic medical center in Canada; • Data: pretreatment PSA, clinical TNM stage, primary and secondary biopsy GS, cumulative length of cores and of cancer (mm in all cores), % positive cores, tumor volume at final pathology**;**	**IPCA:** • Pathologically confirmed in 65 men (5.7%); • 200 boot-strap corrected new nomogram accuracy 90% vs. 81% for older Epstein nomogram; • Cut-off analyses of patients classified as high probability IPCA by both nomograms: 63% and 45% had aggressive disease (Gleason 7-10). **Conclusions:** *"Despite a high accuracy, currently available models for prediction of IPCA are incorrect in 10% to 20% of predictions. The rate of misclassification is even further inflated when specific cutoffs are used. As a consequence, extreme caution is advised when statistical tools are*

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	• PCA defined as organ-confined, tumor volume < 0.5cc; and no Gleason 4 or 5 patterns; • Model development and validation in same patients.	*used to assign the diagnosis of IPCA."*
USPSTF (2008)	**Recommendation statement: screening for prostate cancer:** • RCTs of benefits of prostate cancer screening; cohort and cross-sectional studies of psychological harms of false-positive PSA results; and evidence on natural history of PSA-detected cancers published since 2002 statement	**Detection: "**convincing evidence" that PSA screening can detect some cases of prostate cancer. **Benefits of detection and early treatment:** • **"**Inadequate evidence" in men< 75 years; • Adequate evidence that benefits for men > 75 are small to none. **Harms of detection and early treatment:** • "convincing evidence" that treatment of screen-detected cancer causes moderate-to-substantial harms (erectile dysfunction, urinary incontinence, bowel dysfunction, death); • Harms are important because some men with screen-detected cancers would never have developed symptoms; • Adequate evidence that screening causes at least small harms (pain and discomfort of biopsy, psychological effects of false-positive PSA results. **Conclusions:** *"The USPSTF concludes that for men younger than 75 years, the benefits of screening for prostate cancer are uncertain and the balance of benefits and harms cannot be determined.* *For men 75 years or older, there is moderate certainty that the harms of screening for prostate cancer outweigh the benefits."*
Wilt (2008c)	**Hospital and surgeon volume-outcome association for radical prostatectomy:** • Multiple databases, 1980-November 2008; • Quality rating scale (0-5) applied to articles; • Included: English-language controlled studies evaluating the association between provider volumes and patient outcomes for radical prostatectomy; • Outcomes: mortality, postoperative complications, failure of cancer control; • Results pooled using random effects models.	**17 observational studies (235,763 patients) included:** • Hospitals with volumes > mean (43 procedures/yr) had lower surgical mortality (rate difference, 0.62; CI 0.47-0.81) and morbidity (rate difference, -.97; CI, -25.- 3.6); • Teaching hospitals had 18% (CI, -26, -9) lower rate of complications; • Surgeon volume was not significantly associated with surgical mortality or positive surgical margins; • Rate of late urinary complications or long-term incontinence was 1.2% lower for each 10 additional; procedures performed by a surgeon annually; • LOS was lower, corresponding to surgeon volume. **Conclusions:** *'Higher provider volumes are associated with better outcomes after radical prostatectomy. Greater understanding of factors leading to this volume-outcome relationship, and the potential benefits and harms of increased regionalization is needed."*
Chen (2009a)	**Provider case volume and brachytherapy outcomes:** • Claims analysis: Medicare enrolled men > 65 years living in SEER surveillance areas, diagnosed and received brachytherapy, 1991-1995; • Case volumes for physicians and hospitals, 1991-2001; • Outcomes: recurrence; prostate cancer death; all-cause	**5595 men for whom radiation oncologist and hospital could be identified:** • Men who were older, non-white, lower income, unmarried, living in non-urban areas or had more co-morbidities were more likely to use lower volume providers; • Physician volume not associated with complications after brachytherapy, but higher volume physicians had lower rates of combined complication diagnoses and procedures (OR, 0.94/100 cases; p<0.01); rate of prostate cancer death (HR, 90.80/100 cases; p = 0.03); and borderline

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	death; 2-year complications.	significant decrease in all deaths (HR, 0.95/100 cases; p = 0.05); • NS association between hospital volume and recurrence, cancer death, or all deaths. **Conclusions:** *"Men treated with brachytherapy by higher volume physicians were at lower risk for recurrence and prostate cancer death, and showed a borderline decrease in total deaths. We did not observe a clear relationship between provider volume and complications following treatment."*
Roemeling (2007)	**Case series:** **Active surveillance in men with screen-detected localized cancer:** • 3 screening rounds of ERSPC Rotterdam, 1993-2006; • Recruitment and surveillance according to decision by patients and physicians; • Baseline characteristics and outcome for screen-detected cancers.	**278 men with screen-detected cancer:** • Median age 69.8 (25-75); PSA, 3.6 ng/ml (3.1-4,8); T1c in 220 (79.1%); T2 in 58 (20.9%); • During median 3.4 yr FU: 103(44%) had negative (> 10 yr) PSA doubling time; • Men detected at re-screening more likely to be on active surveillance and have more beneficial characteristics; • Deferred treatment elected in 82 cases (29.0%); • Overall survival 89% at 8 yrs; cause-specific 100%. **Conclusions:** *"This report shows a beneficial, although preliminary, outcome of screen-detected men managed on active surveillance. Men were more likely to be on active surveillance if the disease was detected at repeated screening. The report also shows that an important proportion of men have prolonged PSA doubling times, although the value of this parameter has not been established in untreated men."*
MacDonald (2007)	**Systematic review (Cochrane methods)** **PFMT to improve UI after RP:** • Multiple databases, 1966-2006; • English-language RCTS reporting clinical outcomes (return to continence by questionnaire or other objective measure); controlled by placebo, usual care; no care; or active treatment; • Quality assessment: blinding of subjects or outcome assessors; ITT analysis	**11 trials (1028 subjects):** • Duration 3-12 months; • In one trial of 300 subjects: PMFT achieved continence more quickly (1, 3, 6 months) than no PFMT; • Men receiving biofeedback-enhanced PFMT more likely to achieve continence or have no continued leakage than those with no training at 1-2 months after surgery (relative benefit increase 1.54; CI, 1.01-2.34; four trials); • Relative benefit increase, 1.19 (CI, 0.820-1.52; 5 studies) was no longer significant after 3-4 months; • Biofeedback enhanced PMFT was comparable to written/verbal instruction; • Extracorporeal magnetic innervations (Japan; not available in US) and electrical stimulation more effective than PFMT at 1-2 months (1 trial), but NS difference≥ 3 months. **Conclusions:** *"Based on available evidence, PFMT with or without biofeedback enhancement hastens the return of continence more than no PFMT in men with UI after RP. Additional trials are needed to confirm whether extracorporeal magnetic or electrical stimulation are effective conservative treatment options."*
Ilic (Cochrane: 2006) and Ilic (abstract;	**Cochrane review** **What is the efficacy of screening asymptomatic men for prostate cancer in reducing all-cause and prostate cancer-**	**2 RCTs (55,512 subjects):** • Both RCTs had methods weaknesses; re-analyzed by meta-analysis and intention-to-screen: no statistically significant difference in prostate cancer mortality (RR, 1.01; CI, 0.80-1.29);

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2007)	**specific mortality?** **What is the impact of screening on QoL and adverse events?** **What are cost-effectiveness, cost-utility, and cost-benefit of mass screening?** • Multiple databases plus hand searching; 1966-January 2006; all men enrolled in studies (RCTs, quasi-randomized, or controlled trials) of prostate cancer screening without exclusion for demographics or language of publication; • Interventions: DRE; PSA (total, dynamics, percentage free, complex);TRUS biopsy; • Outcomes: incident cancers, stage and grade at diagnosis; metastatic disease at FU; QoL; Costs associated with screening programs; harms of screening (adverse outcomes from false positive or negative results and impact on resulting treatment); • Included: trials, quality assessment by randomization, blinding, allocation concealment, completeness of FU, intention-to-screen analysis.	• Neither RCT assessed effects on QoL, all-cancer mortality, or cost-effectiveness. **Conclusions:** *"Given that only two randomized controlled trials were included. And the risk of bias in both trials, there is insufficient evidence to either support or refute the routine use of mass, selective or opportunistic screening compared to no screening for reducing prostate cancer mortality. Currently, no robust evidence from randomized controlled trials is available regarding the impact of screening on quality of life, harms of screening, or its economic value. Results from two ongoing large scale multicenter randomized controlled trials that will be available in the next few years are required to make evidence-based decisions regarding prostate cancer screening."*
Andriole (2009)	**PLCO** **First prostate cancer mortality results:** • RCT: 1993-2001; • 76,692 men received annual screening (PSA for 6 yrs, DRE 4 yrs) vs. 38,343 controls receiving usual care; • FU up evaluations determined by individual patients and physicians; • Some control patients received screening tests.	**Compliance in screening group:** 85% for PSA; 86% for DRE; **Screening in controls:** • 40% first year, 52% in 6th (PSA); • 41% and 46% for DRE. **7 years FU:** • Cancers/10,000 screened: 116 (2820 cancers); 95 in controls (2322 cancers); rate ratio, 1.22 (CI, 1.16-1.29); • Prostate cancer death: 2.0/10,000 person-yrs in screening group; 1.7 in controls; rate ratio, 1.13 (CI, 0.75-1.70); • Data at 10 yrs 67% complete and consistent with 7 years. **Conclusions:** *"After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups."*
Gosselaar (2009)	**ERSPC Rotterdam** **Are men with initially suspicious DRE, PSA≥3.0ng/ml, and benign biopsy at higher risk for significant cancer at screening?** **Is a modified screening interval for such men warranted?** • Rotterdam section: men biopsied (1993-2000) at initial screening with benign result;	**2218 men received biopsy:** • Prostate cancers at 4 yrs: 27 (6%) in men with initially suspicious DRE; 103 (6%) in men without suspicious DRE (P = 0.99); at 8 yrs: 10%; 10%, respectively (P = 0.88); proportion clinically significant, 2%; 3%; • Suspicious DRE at initial screen not a significant predictor for detecting cancer at 4 yrs (OR, 1.15; p = 0.59; or 8 yrs (OR, 1.41; p = 0.43).

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	• PSA every 4 years: ≥3.0ng/ml prompted lateralized sextant biopsy; • Measurements: number and characteristics of lesions found at repeat screening or as interval cancers; presence/absence of suspicious DRE at first screen.	**Conclusions:** *"During a follow- up of 8 yr after initial cancer-negative biopsy, an initially suspicious DRE did not influence the chance for detection of cancer or significant cancer at later screens. An adaption of the rescreening interval on the basis of initial DRE-outcome is not warranted in future population-based screening for prostate cancer."*
Laurila (2009)	**Cross-sectional** **Analysis of Finnish screening trial subjects for biologic aggressiveness of tumors:** • 80,458 men: 32,000 randomized to screening; 48,000 controls; • Interval cancers and cases among non participants identified through Finnish Cancer Registry; • Random samples of screen-detected cases (126/534 in round 133/508 in round 2) and control cases (133/863); plus 92 interval cancers; • Expression of Ki-67 determined in 72% of cases.	**Total 570 cancers:** • 82 **(**14%) localized; 89% of those were Gleason 6; • Proportion of focal tumors differed significantly among groups (p = 0.04); • Screening round 1 & 2 plus interval cancers: significantly fewer bilateral (p>0.001); • Bilateral cancers twice as frequent in controls (OR, 2.88; CI, 1.66-5.01); three times as frequent in interval cancers (OR, 4.20; CI, 2.20-8.03); • Ki-67 associated with GS; high Gleason stained most frequently and significantly different among groups (p = 0.039). **Conclusions:** *"Our results indicate that the biological aggressiveness of screen-detected prostate cancers is more often lower than in the control arm and non participants. Further, cancers detected in the second screening round show fewer aggressive features than those from the first round. Further, few interval cancers have characteristics indicating aggressive behavior, which suggests that a 4-year interval mat not be too long in prostate cancer screening. Measurement of proliferation might be used as an optional aid in the decision of treatment of screen detected low grade cancers."*
Schröder (2009)	**ERSPC:** • RCT: PSA screening on average every 4 yrs vs. non-screened; • 182,000 men identified through registries in 7 European countries; 162,243 in core age group (55-69 yrs); • Mortality FU ended on December 31, 2006.	**72,952 screening group; 89,453 control:** • 82% of screening group accepted at least one offer of screening; average 2.1 tests/subject; • 16.1% (11.1-22.3) of tests positive; average compliance with biopsy recommendations, 85.8%; • Of men who had biopsy following elevated PSA result: 78% false positive; • 5990 cancers in screened group, 4307 in controls: cumulative incidence rates, 8.2% and 4,8% at median FUY 9 yrs; • PPV of biopsy, average 24.1% (18.6-29.6); • Cumulative incidence of local cancer higher in screened group than controls; • Rate ratio for death in screened group Vs controls, 0.80 (CI, 0.65-0.98; adjusted P = 0.04); • Absolute risk difference, 0.72 death/1000 men: 1410 need to be screened and 48 additional cases treated to prevent one prostate cancer death; • Men actually screened during first round (excluding non-compliant subjects: rate ratio, 0.73 (CI, 0.56-0.90). **Conclusions:** *"PSA-based screening reduced the death rate from prostate cancer by 20% but was associated with a high risk of over-diagnosis."*
Grubb (2008)	**PLCO trial:** **First four rounds for prostate: Does annual PSA and DRE reduce mortality?** • Abnormal PSA: > 4.0ng/ml; nodularity or induration on	**38,349 randomized to screening arm:** • 86% non-Hispanic white; 60%< 65 yrs; 25% had history of enlarged/inflamed prostate or other prostate problems; • Compliance similar for both tests: majority receiving either received both;

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	DRE; • Men 55-74 years at multiple US centers, 1993-2001; • Exclusions: previous prostate cancer or prostatectomy; use of finasteride during previous 6 months; (from April 1995-)> one PSA test in previous 3 yrs • FU of abnormal results at discretion of patient and physician.	• Compliance decreased over time; 89.4% at baseline to 85.1% at T3; • PSA positive rates (7.7%-8.8%) and DRE positive (6.8%-7.6%) relatively constant over time; • PPV of PSA > 4.0ng/m; decreased from 17.9% to 10.4-12.3%; PPV of DRE alone 2.9-3.6%; • Cancer diagnosed in 1902 (4.9%): screen –detected cancers at baseline more likely to be stage III/IV (5.8%) and Gleason 7-10 (34%) at later screenings. **Conclusions:** *"The present findings on serial prostate screening are similar to those reported from other multi-round screening studies. Determining the effect of PSA screening on prostate cancer mortality awaits further follow-up."*
Aus (2007)	**Cross-sectional:** **Risk of diagnosis of advanced cancer in screened vs. control subjects (ERSPC Göteberg branch):** • Random assignment to PSA-based screening vs. control groups for men born 1930-1944 (50-66 yr) in Göteberg Sweden, 1995-2004; • Metastatic prostate cancer risk evaluated at 10 yr FU.	**1252 cases of prostate cancer during study period:** • 810 in screened group, 442 in controls; • Men randomized to screening had 1.83 –fold increased risk of diagnosis compared to controls; • Majority of tumors in screened group were localized: absolute numbers of men with intermediate- or high risk features lower in careened group; • Risk of diagnosis with metastatic disease reduced 48.9% by screening (24 cases vs. 47 in controls; p = 0.0084). **Conclusions:** *"Biennial PSA screening reduces the risk of being diagnosed with metastatic prostate cancer, the first prerequisite for achieving decreased cancer mortality in younger men. This putative benefit is balanced by a 1.8-fold increased risk for diagnosis of prostate cancer."*
Norderhaug (2003)	**SINTEF review:** • Cochrane and HTA databases,1966-2000: systematic reviews on prostate brachytherapy plus clinical studies and ongoing trials; • Included: studies comparing clinical outcomes for brachytherapy vs. EBRT or WW; • Quality assessment: acceptable if control or comparison group; grades, 1 (RCT); 2 (controlled trial, cohort, or case-control); 3 (series or cross-sectional).	**No RCTs or large prospective studies available:** Evidence for effectiveness of brachytherapy restricted to observational comparisons with RP or EBRT; **BT vs. RP comparisons:** • 6 studies available, only 1 of acceptable quality; that one also used non-comparable groups but analyzed by risk (no difference in 5-yr PSA-relapse free survival); • No acceptable studies compared QoL. **BT vs. EBRT comparisons** (5) **:** • No difference in 5- or 7- yr PSA free survival; • 5-yr difference in complication rates: 11% of BT vs. 6% of 3-D conformal radiation patients reported grade 2 proctitis; changes in sexual function not reported. **Brachytherapy in combination with EBRT**(2/6 studies included): • One case-control: better 5-yr PSA-free survival with BT plus EBRT; • One observational study: fewer rectal complications for BT. **Cost and cost-effectiveness:** no acceptable studies available. **Conclusions:** *"The evidence on the clinical effectiveness of prostate brachytherapy is poor. There is a lack of knowledge from RCTs or large prospective comparative studies on the clinical effectiveness*

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		of brachytherapy compared with radical prostatectomy or external beam radiation. According to the few comparative studies that have been reported, prostate brachytherapy was comparable to radical prostatectomy and external bean radiation with respect to cancer control. There was no evidence for any differences in disease-free survival for a follow-up of 5-10 years between brachytherapy, external beam therapy or radical prostatectomy. Common complications after brachytherapy were urinary tract irritation, impotence, and proctitis. There was no evidence from comparative studies that the complications seen after brachytherapy were less frequent or severe than those seen after external beam radiotherapy or radical prostatectomy. Long-term complications, however, are not known. None of the included studies had valid data on overall survival."

VA TECHNOLOGY ASSESSMENT PROGRAM

Mission Statement

To enhance the health of Veterans and the nation by providing and fostering technology assessment for evidence-based health care

Values

Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

Objectivity in evaluating and presenting research evidence

Commitment to continuous quality improvement and to the guiding principles of evidence based practices

Flexibility in responding to changes in VA and the larger healthcare environment

Innovation in designing products and their dissemination to best meet VA's needs

Accessibility of products and services